



Memorandum

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From: Marc Walton, MD, PhD; OTRR/DCTDA
Subject: Medical Officer Review
Through: Karen Goldenthal, MD, Director, OVRR/DVRPA

**PLA 91 - 0184
Complete Response Submission**

Allergan, Inc.

**BOTOX
Botulinum Toxin Type A
For Treatment of Cervical Dystonia**

Clinical Review

OVERVIEW

Allergan, Inc. has submitted a complete response to a Complete Review Letter (known at that time as a Not Approvable Letter) for their supplemental marketing application, PLA 91-0184 on June 9, 1999 for botulinum toxin type A neurotoxin complex for use in the treatment of cervical dystonia.

The initial submission of PLA 91-0184 occurred in March 1991, with an amendment submission (a literature report of an additional study) in March 1994. The Complete Review Letter was sent on December 21, 1995 to Allergan, which stated that the submitted information was inadequate to provide marketing approval for the cervical dystonia indication, and that an additional phase 3 clinical study was required to enable further consideration of the application.

Allergan has conducted such a study, and submitted it along with additional other studies subsequently determined to be necessary during IND discussions. Allergan has proposed the supplemental indication be stated in the labeling as: Botox is indicated for the treatment of cervical dystonia (spasmodic torticollis) in adults.

History of the sPLA and Scope of the Review

A long clinical development program has been conducted. The initial studies of Botox in the treatment of cervical dystonia were conducted prior to Allergan's acquisition of the product, and prior to the initial marketing approval for Botox. These studies were the basis of the original supplemental PLA submission in 1991. These studies were deemed to be seriously flawed in design and conduct and inadequately documented. There were 5 controlled trials and 3 open label treatment studies in this initial group. These studies have not been further reviewed at this time. A brief orientation to these studies is contained in an appendix of this review document. However, for detailed information regarding these studies, the comprehensive reviews dating from the initial submission of Dr. L. Teague (CBER) and Dr. Collins (CDER Collaborative Review) should be consulted, as well as the CBER Statistical Review of those studies.

There are four studies presented in this CR response. One study is the phase 3 efficacy trial, and is accompanied by a companion non-treatment study to assess the evaluation tool employed in the phase 3 study. Subsequent to completing the phase 3 study, Allergan changed the source of the marketed toxin from a single batch produced in 1979 (the only source of Botox in the U.S. since the initial marketing approval) to a batch produced in a newly constructed toxin manufacture facility. This new toxin, designated [X]-----, had received marketing approval in late 1997 for the currently approved indications. However, in the studies supporting [X]----- distribution concern regarding an increased risk of regional toxin spread had been raised. Consequently Allergan was asked to address this potential difference in safety profile with additional studies. Two additional studies have been submitted that address the safety of the currently marketed Botox product in this indication. These four studies are the focus of this review.

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INTRODUCTION

Botulinum Toxins

Clostridia botulinum is an anaerobic bacterium that produces a neurotoxin. The clinical disease botulism and the association with tainted foods was described in the late 18th-early 19th centuries, from whence the name derives; German blood sausage was the most highlighted source, and *botulus* the Latin for sausage. The organism was first isolated and identified by E. van Ermengem in the late 19th century and shown to produce a toxin. Different strains of *C. botulinum* have been identified to produce 7 different types of this neurotoxin, designated types A through G, initially distinguished largely as different serotypes. *C. butyricum* produces a neurotoxin similar to type E, and *C. baratii* a toxin similar to type F (but neither are identical). Botulinum toxin has been called the "most poisonous poison", and thought to be the most lethal substance known (on a per molecule or per weight basis). Types A, B, and E are thought to account for the great majority of cases of human poisoning. The toxin is heat labile.

The toxin proteins of all types are synthesized by the bacillus as a single chain polypeptide of MW approximately 150 kD. A selective proteolysis step (nicking) is important in achieving the fully active toxin molecule with two chains (designated the heavy and the light chain) joined by disulfide bonds.

The toxins are all zinc metalloproteases, and their mechanism of toxicity is generally similar. All bind at specific receptor sites on cholinergic presynaptic terminals, although the specific receptor sites do not appear to be identical for all of the serotypes. The toxins are taken up by endocytosis, and in a process dependent upon a transmembrane pH difference, form pores in the endocytic vesicle membrane through which the light chain (possibly with some of the heavy chain) translocates into the cytosol. Once in the cytosol the protease toxin is active and each cleaves a specific protein critically involved in the neurotransmitter vesicle release process. There are three synaptic terminal proteins identified which have the specific proteolytic site for toxin types A through F (toxins A, E on SNAP-25, B,D,F,G on Synaptobrevin [VAMP], and type C on Syntaxin).

Thus, toxin effects result in the failure of transmission at the neuromuscular junction. The toxin's effects are most prevalent at the neuromuscular junction, but have some effects also at the autonomic cholinergic terminals. Central nervous system botulinum toxin effects are not prominent when toxin is administered in the periphery, but in vitro the toxin is active in synaptosome preparations from CNS.

Consistent with the loss of neuromuscular junction transmission, clinical botulism consists of a flaccid paralytic disease. Symptoms stemming from ocular muscle paralysis are often the first noticed. The most threatening aspects are the loss of pharyngeal and diaphragmatic muscle function leading to risks of respiratory failure and aspiration, and are the primary causes of death in botulism patients. There is no known mechanism to reverse the synaptic failure once it has occurred. Reversal of the paralysis occurs only through natural means, and appears to occur by sprouting of new nerve terminals.

Botulinum toxin functions by producing a state of functional denervation. While immediately the nerve endings remain juxtaposed to the muscle (the neuromuscular junction, NMJ), neuromuscular transmission failure occurs, and the muscle responds as if actually denervated. Acetylcholine

receptors begin to appear in a diffuse pattern along the entire muscle fiber, not localized to the NMJ. The nerve however, remains viable, and responds with sprouting of new nerve terminals. These form new neuromuscular junctions with the muscle fibers. Several months can be required to develop adequate sprouting to replace the disabled terminals. This sprouting and formation of new NMJ is responsible for the recovery of muscle function, and the consequent loss of benefit of the toxin over the subsequent months.

The type A neurotoxin is presently the only type in widespread clinical use and commercially available. However, several other serotypes are under investigation by various manufacturers. The Type B toxin developed by Elan Pharmaceuticals has been investigated for use in the treatment of cervical dystonia as well, and a BLA submitted to CBER (BLA 98-1396).

Potency of botulinum toxins is generally assessed with a mouse intraperitoneal injection assay, with death as the read-out. The assay indicates activity in Units or Mouse Units, with 1 U of activity defined as the LD50 dose. However, the manufacturers of the different toxins use slightly different procedures in conducting the assay, and the medical literature indicates that these differences can lead to dramatic differences in the apparent potency. Thus, any clinical differences observed in the number of Units of toxin to achieve specific clinical effects may be partly related to differences in the laboratory assay used to calculate the potency. There are likely to be differences in the affinity of each toxin serotype for its receptor, as well as different receptor numbers per terminal for the different receptor types. These differences may contribute to different clinical characteristics for the different toxin types.

There are also known species differences in sensitivity to the toxins. Guinea pigs appear to be particularly sensitive to botulinum toxin toxicity (compared to some other small animals) but rats seem particularly less sensitive to Type B toxin than to Type A. Therefore, extrapolation of any relative doses for efficacy or toxicity between toxin types based on animal comparisons of effect between toxin types must be done with caution.

Botulinum Toxin Type A

The history of the development of botulinum toxin type A for clinical use has been recently reviewed by E.J. Schantz and E.A. Johnson, two investigators who played central roles in the development of modern production and purification processes of botulinum toxin type A. Interest in botulinum toxin and protection methods increased as a result of war-related concerns, and the NAS developed an investigational program during the early 1940s. Scientific research interest continued after World War II ended, and the type A toxin was produced and purified in sufficient quantities to be available to investigators at many sites. The investigation of clinical uses of botulinum toxin stems from work of Dr. A. Scott, who initiated clinical studies of botulinum toxin type A in strabismus in the late 1970s. Subsequent to this, investigations by Scott and others in a variety of clinical disorders generated wider interest in the clinical use of the toxin (see following section).

As described above, botulinum toxin type A is synthesized by the bacillus as a single polypeptide chain, and cleaved into two components (by removal of 10 amino acid residues), of MW 53 kD (light chain) and 97 kD (heavy chain), bound by disulfide bonds. Along with the toxin protein are also synthesized several other proteins that are co-purified with the toxin. These consist of a 130

kD non-hemagglutinating protein, and several hemagglutinins, ranging from 14 to 48 kD. The entire purified composite has a MW of 900 kD, and is named the Botulinum Toxin Type A Neurotoxin Complex by Allergan, Inc, and given the internal designation [-----]. Only the 150kD toxin chain is required for toxicity. The other proteins may have effects on stabilization of the toxin, but this has not been well demonstrated.

Potency of botulinum toxin is tested by a mouse intraperitoneal injection assay, from which a LD50 value is obtained. Potency is described in "mouse Units", where 1 U is the estimated dose producing death within 72 hours in 50% of the mice. As is not uncommon with this type of assay biological potency, it is dependant upon a variety factors, including the specific animals used and the details of how the toxin is diluted (or reconstituted when working from lyophilized vials). These toxicity assays are also made more difficult by the very small amounts of toxin protein used and the very steep dose-response curve for type A toxin. The range from 0% to 100% lethality can spanned by a factor of 2 in dose.

The lethal dose in humans has not been directly determined. In several different studies of IM injection into monkeys, the LD50 has been estimated at approximately 40U/kg (with a similar estimate for IV administration). In these studies, the dose response curve is again seen to be quite steep, with a 2-fold range of doses nearly spanning the none to complete lethal range.

Botulinum Toxin Supplies in Clinical Use

At the present time, only Botulinum Toxin Type A is in commercial distribution in the western hemisphere. Botulinum toxin type A is commercially available in the U.S. at the present time only from Allergan. In the United Kingdom and Europe, type A toxin (Dysport) manufactured by Porton (in association with Speywood) is available as well as toxin manufactured by Allergan. These toxins are also commercially available in other countries.

The toxin sold in the U.S. by Allergan from initial approval through November 1997 was finish manufactured from a single bulk batch originally manufactured by E.J. Schantz in November of 1979, and referred to as Batch □---- (1[-- mg total). A different bulk batch, manufactured in 1988 (and designated as Batch □----), is sold by Allergan in other parts of the world. While they are believed to have been manufactured from the same strain of *C. botulinum*, comparability of the toxin in the two lots has not been rigorously evaluated. The specific potency of the □---- botulinum toxin type A complex as manufactured by Allergan is approximately [----- U/mg of complex (approximately 30 U/ng).

A new production facility was constructed by Allergan in Campbell, CA. In November 1996, batch □----- was produced, and was the source of bulk material proposed for clinical use in the PLA Supplement 97-1086. Lot □----- consisted of 1[----- of bulk, purified toxin complex, and has a specific potency of [----- U/mg. Finished vials contain 4.7 ng of toxin complex, 0.5 mg albumin, and 0.9 mg NaCl, in a lyophilized form. Toxin is reconstituted with preservative free saline. Vials are labeled as containing 100 U of toxin complex, with manufacturing specifications allowing a range of [----- U in the finished vial lot. Note that the vial content of toxin calculates to 146 U (for 4.7 ng); this disparity is due to apparent loss of potency in the finishing, lyophilization, and reconstitution process. This new toxin was approved for distribution in November 1997. However, there were indications that the two toxin bulks did not produce identical clinical performance in use. While both toxins appeared to be generally similar in efficacy in

blepharospasm, the new bulk, □----- produced a notably higher rate of the adverse event of ptosis, which is believed to be related to regional spread of toxin after injection. Therefore, safety issues related to regional spread cannot be extrapolated from performance with □---- toxin to performance of □----- toxin.

The toxin manufactured by Porton is from a different source of the organism. The clinical potency of the type A toxin sold by Porton may be different; there is large difference (factors of 3 to 5) in the number of vial-labeled mouse-LD50 units used for comparable clinical effect. Some of this difference may be due to the specifics of the different protocols used by each manufacturer for the mouse LD50 potency assay, and the specifics of the reconstitution for the assay are different than reconstitution procedure for clinical use. However, the mouse intraperitoneal LD50 assay may also not be entirely sensitive to potency differences that are relevant to actual clinical use, which is intramuscular injection. Several laboratories have published in the medical literature indicating that both issues may be operative, and combined can account for the apparent difference in mouse-units needed for similar clinical effect with the two different toxin sources. As one consequence of this, dose-related safety records based upon published literature reports need to carefully consider the source of the toxin.

Labeled Clinical Indications of BOTOX

Allergan submitted PLA 85-0227 which resulted in the marketing approval of botulinum toxin type A complex for the treatment of strabismus and blepharospasm associated with dystonia. The safety and efficacy data were derived largely from uncontrolled studies, but consisted of a substantial number of different such studies, with 2322 strabismus patients, and 1684 blepharospasm patients. Since this initial approval in 1989 there have been multiple additional publications (also largely uncontrolled) in the medical literature further supporting the favorable risk-benefit judgement in this indication. These two disorders constitute the only U.S. approved indications for BOTOX. In other countries, BOTOX has additional indications, including approvals for cervical dystonia in some countries.

Off- Label Use

There is considerable use of BOTOX in the U.S. for indications other than those described in the label. In 1990 a Consensus Conference convened by NIH discussed the clinical uses of botulinum toxin. This consensus conference endorsed the use of botulinum toxin in the disorders described in the U.S. label for BOTOX, but also endorsed its use in cervical dystonia, Meige syndrome (orofacial dystonia), and encouraged further investigations in several additional disorders. Since that time, numerous reports have appeared in the medical literature supporting toxin use in other focal and segmental dystonias, limb spasticity, GI disorders such as achalasia and anismus, and cosmetic use for reduction of frown lines and other facial skin folds.

An important difference in these uses is that the risk benefit comparison has not been as well documented to date, and may involve usage in a manner inherently more risky. Cervical dystonia is perhaps the most clear example of this. Reported doses of toxin used for cervical dystonia are up to 5 times higher than typical doses for blepharospasm, and are injected into a region surrounding the pharynx, placing adequate pharyngeal function at specific risk.

Due to the difference in the doses used for the different types of disorders, and the numbers of patients available with each disorder, it is estimated that in the U.S., the majority of BOTOX use is for these off-label uses.

Cervical Dystonia

[Note to reader: While the general discussion regarding the disease is drawn from multiple sources, including published textbooks, it is most directly from the cervical dystonia discussion in the electronic textbook Neurobase, Gilman S, Goldstein GW, and Waxman SG, eds; Arbor Publishing Corp., 1999 edition]

Cervical dystonia is a syndrome consisting of abnormal head and neck posture with sustained or intermittent movements, and is commonly associated with pain. Previously known as "spasmodic torticollis," cervical dystonia was defined as "an involuntary hyperkinesis involving the muscles of the neck primarily on one side" (Foltz et al 1959). Earlier in this century, the etiology of cervical dystonia was controversial, regarded as psychogenic by some physicians. However, in recent times the organic nature of cervical dystonia has been widely accepted.

Patients with cervical dystonia have involuntary head and neck movements resulting in abnormal postures. The most prominent feature is usually sustained deviation of the head to one side. Terms such as "torticollis," "anterocollis," and "retrocollis" describe the direction of head movement laterally, forwards, and backwards, respectively. There may be lateral flexion of the cervical spine, or horizontal displacement of the head. There is frequent associated asymmetric hypertrophy of neck muscles, the sternocleidomastoid being most commonly involved. Superimposed on the sustained abnormal posture may be fast components in the form of spastic jerks or head tremor, but these are not universally present. Neck pain is a common feature, present in more than half of patients. This pain is often amongst the most troubling aspect to the patient.

Patients may touch certain parts of their head with their hand, and by doing so they may easily bring their head back straight. This phenomenon is known as "sensory trick" and is helpful in establishing the diagnosis of idiopathic cervical dystonia. Associated postural hand tremor is common, present in about 30%. Typically there should be no contractures, but in patients with a prolonged history of cervical dystonia, there may be fixed deformities in the neck. The abnormal head and neck movements disappear when the patient is sleeping. Swallowing functions may be abnormal, especially in patients with extreme retrocollis.

The etiology of idiopathic cervical dystonia remains unknown. The most accepted theory is that of an abnormality in certain parts of the basal ganglia or brainstem. Since putamenal lesions have been shown to cause contralateral dystonia, the anatomical substrate may be related to this structure or its pathways. However, no definite pathological abnormality has been defined.

The relation with trauma is unclear. Clinically, torticollis occurring shortly after neck injury differs from typical idiopathic cervical dystonia in that there is usually no improvement during and after sleep, and no help by "sensory tricks" (Truong et al 1991).

The prevalence rate has been estimated as approximately 9 in 100,000 (Nutt et al 1988). The overall incidence rate was estimated as 1.2 per 100,000 (Claypool et al 1995). Other sources estimate the US population with CD to be approximately 80,000.

The peak age of onset is from 40 to 49 years, with the majority of patients having onset of the disease between the age of 30 to 55, though it may involve the extremes of ages. A slight female

preponderance of approximately 65% women to 35% men has been reported, with various published studies reporting ratios of 1.5 to 1.9 (e.g., Jankovic J., et.al., 1991, *Neurology* 41:1088-1091; and Chan J., et.al., 1991, *Movement Disorders* 6:119-126).

The diagnosis is usually made clinically. There is no confirmatory test for cervical dystonia and excluding secondary causes is most important. Spontaneous remission can occur in a minority of patients, usually taking place within the first year of symptoms and with decreasing frequency as the illness becomes more chronic. The majority of patients will have symptoms that usually remain static 5 years after the onset.

Current Management of Cervical Dystonia

There are no currently approved treatments for cervical dystonia in the U.S. Oral medications have generally been disappointing in their effectiveness. High-dose anticholinergic drugs such as trihexyphenidyl have been described to be effective in a small number of patients. Treatment with both muscle relaxants (such as Lorazepam and other benzodiazepines) and spasmolytic agents (such as Lioresal) is a popular combination. Other drugs tried in cervical dystonia include cholinergic, dopaminergic, and antidopaminergic drugs. These may be helpful in individual patients, but the effects may be transient, lasting only a few months, and do not uniformly benefit the broad population of patients.

Botulinum toxin injected intramuscularly into the dystonic neck muscles is currently regarded as the mainstay of relieving symptoms of cervical dystonia. Over the past decade or so many clinical investigators have conducted small studies of varying quality with one of the marketed botulinum toxin Type A products. Frequently, but not uniformly, they have reported favorable results. A National Institute of Health Consensus Development Conference in 1990 issued a statement that BOTOX was regarded as an accepted therapy for treatment of CD. In the US, only one brand of botulinum toxin, BOTOX, a Type A toxin, is commercially available. BOTOX is not currently labeled for treatment of cervical dystonia, and has significant off-label use in the US for these patients. BOTOX is also approved for marketing in Canada, Europe, and numerous other countries.

In many of these countries, but not all, the approved uses include cervical dystonia. A second type A toxin, Dysport (manufacturer previously known as Speywood, now Ipsen) is also marketed in Europe, and is also widely used in Europe for treatment of cervical dystonia. The two toxins are not equivalent nor interchangeable on a unit for unit dose basis. Development of antibodies rendering the toxin ineffective is a concern for long-term usage.

Surgical treatments include thalamotomy, myotomy and rhizotomy, and selective rhizotomy. Varying success has been reported with these techniques, but the results are not uniformly favorable.

Adverse Effects of Botulinum Toxin in Treatment of Cervical Dystonia

The major concerning adverse effect reported in the literature with use of botulinum toxin Type A for treatment of cervical dystonia has been dysphagia. Many investigators have attributed this to spread of toxin locally to pharyngeal muscles adjacent to muscles injected with the toxin. This hypothesis as a source of adverse effects is supported by preclinical studies showing such local spread to adjacent muscles and by observations in treatment of forearm dystonia where EMG localization allowed precise placing of the injections, and specific non-injected but adjacent

muscles can be reliably identified and assessed. These adjacent muscles demonstrated loss of strength in 63% of subjects (n=40, Ross MH, et.al., 1997, Muscle and Nerve, 20:593-598).

Most subjects in published studies have had only mild to moderate severity dysphagia. Nonetheless, some subjects do discontinue repeat injection sessions due to the dysphagia. However, occasional subjects in studies have needed nasogastric feeding tubes until improvement of swallowing. This adverse event has consistently resolved over time (Stell R, et.al. 1988, JNNP 51:920-3). Other studies have reported subjects who required iv fluid therapy for severe dysphagia, with aspiration changes observed on chest xray.

Anderson reported use of Dysport in 107 subjects, with repeat injections for a total of 510 treatment sessions, of which 2% of treatments had severe dysphagia. Two treatment sessions lead to hospitalization for assisted hydration (duration unstated) and two other sessions lead to substantial weight loss. One subject developed aspiration pneumonia. No deaths were reported. The dysphagia was believed to be dose related, especially the dose injected into the SCM muscle. Anderson also reported an event of leg weakness in a subject with a prior history of polio, suggesting hematogenous spread also and sensitivity of muscles in this patient. (Anderson TJ, et.al., 1992, J. Royal Soc Med. 85:524529)

There have been rare reports of severe dysphagia in subjects with co-existing known as well as unrecognized neuromuscular disease. Tuite and Lang (1996, Neurology 46:846), report 2 subjects with known Machado Joseph Disease who were treated for accompanying cervical dystonia. These subjects developed severe dysphagia which persisted for months, after receiving 320 or 250 U BOTOX. Gastrostomy was required for 6 months in both patients. Emmerson (1994, Mov Disord 9:367) reported a subject with myasthenia gravis treated with botulinum toxin, who also developed severe dysphagia.

Erbguth et.al. (1993, JNNP 56:1235-6) report on a patient treated for blepharospasm with Dysport (8ng) who experienced marked generalized weakness as a result which lead to a diagnosis of paraneoplastic Lambert Eaton Myasthenic syndrome, which had not been clinically evident prior to toxin injection. The authors emphasize that patients with underlying neuromuscular disease are at increased risk of generalized muscle weakness from even low doses of botulinum toxin injected for local effect. Borodic (1998, Lancet 352:1832) reports a similar case of uncovering a diagnosis of myasthenia gravis in a patient where the dysphagia was severe enough to require a gastrostomy for nutrition.

Bakheit et.al. (1997, JNNP 62:198) report a multiple sclerosis patient who received 250 U Dysport which lead to widespread weakness and a patient with multisystem atrophy and existing pharyngeal dysfunction who had been receiving without problems 750 U Dysport for 5 years of repeated injection, who then experienced severe generalized weakness after a regular treatment session. Mezaki et.al. (1996 Neurology 46:845) report on an ALS patient who received 300 U of a Japanese marketed botulinum type A product and had a dramatic increase in weakness.

Taken together, these reports emphasize that patients with neuromuscular disorders may be markedly more systemically sensitive to the generalized effects of local IM toxin injection than patients without such disorders.